IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	George M. Halow
Serial No.	10/194,251
Filed:	July 15, 2002
Art Unit:	1616
Examiner:	Frank I. Choi
For:	Bowel Cleansing Composition

AFFIDAVIT OF MONROE SCHEINER, M.D.

State of Florida

County of Dude

On this day, Monroe Scheiner, M.D. appeared before me, the undersigned notary public. After I administered an oath to him, upon his oath he said:

1. My name is Monroe Scheiner, M.D. I am competent to make this affidavit. The facts stated in this affidavit are within my personal knowledge and are true and correct.

2. I am a physician licensed to practice medicine in the state of Florida. I graduated from the George Washington University School of Medicine with the M.D. degree. I completed an internship and residency in internal medicine and a fellowship in gastroenterology at the University of Miami School of Medicine. I am board eligible in internal medicine and gastroenterology. I am a Clinical Instructor at the University of Miami School of Medicine. I am engaged in the private practice of gastroenterology. In my practice, I have performed thousands of colonoscopies over 35 years.

3. In order for the physician to be able to perform a thorough examination of the large intestine (also known as the colon), the large intestine must be clean and largely free of retained feces. Retained feces can make it difficult for the physician to identify defects in the colon during colonoscopy. In order to remove the stool from the large intestine and provide a clean surface for examination, the patient ingests a bowel cleansing preparation prior to the performance of the colonoscopy. The bowel cleansing preparation "cleanses" the colon of feces resulting in a large intestine largely free of feces. In this environment, a close examination of the colon may be made by the physician. Over the years several methods and preparations have been developed and used to cleanse the bowel of residue in order to permit a through examination of the colon. Most of these methods and preparations involved osmotically inducing a diarrhea which on some occasions was so severe as to result in an electrolyte imbalance in the patient. This electrolyte imbalance is potentially harmful to the patient.

As new methods and preparations have been developed for bowel cleansing prior to colonoscopy and other intestinal procedures and surgery, each of the new methods or preparations had to be extensively tested for safety and efficacy before wide spread use of the new method or preparation because of the unpredictability of these methods and preparations to safely and adequately cleanse the bowel for colon procedures. Since unpredictability remains in this area of medicine, as new methods and preparations are developed, each will have to be extensively tested to identify the unforeseen issues regarding safety and efficacy.

4. In general, a laxative is not the same as a bowel cleansing preparation. A laxative merely softens the stool making it easier for the stool to transit the colon. A

laxative does not generally cleanse the bowel of stool to permit an adequate examination of the colon by colonoscopy. Likewise, a bowel cleansing preparation would generally not be used as a laxative. The bowel cleansing preparation is time consuming and potentially uncomfortable for the patient. Moreover, using a bowel cleansing preparation as a laxative is unwarranted and excessive.

5. Polyethylene glycol (PEG) is commonly used as a bowel cleansing preparation for colonoscopy. When the term "PEG" is used by gastroenterologists in the context of bowel cleansing in anticipation of a colonoscopy, it is understood that the PEG preparation contains electrolytes such as are found in bowel cleansing preparations such as Golytely®. The inclusion of electrolytes with PEG is necessary to prevent any electrolyte imbalance which may occur during the bowel cleansing procedure.

6. Electrolytes are chemical compounds such as sodium chloride which can dissociate in an aqueous environment into free ions that can conduct an electric current. Those chemical compounds which are electrolytes are composed of a positively charged species and a negatively charged species. In an aqueous medium such as water, the electrolyte will dissociate resulting in free positively charged species and free negatively charged species. The primary positively charged ions or electrolytes are sodium, potassium, calcium, and magnesium. The primary negatively charged ions or electrolytes are chloride, phosphate, and hydrogen carbonate.

7. Electrolytes are important in proper functioning of the human body and all other life forms. Electrolytes are important in the activity of muscles and neurons and establish an appropriate environment in the body to regulate hydration and blood

acidity. A deficiency or imbalance in of electrolytes can result in the failure of muscles to contract or for neurons to transmit impulses from one nerve to another or from one nerve to a muscle. An imbalance or deficit in electrolyte concentration can result in serious cardiac or neurologic complications and result in death.

8. To prevent an electrolyte imbalance from developing while a patient is undergoing a bowel cleansing procedure prior to colonoscopy, electrolytes are added to the bowel cleansing preparation such as Golytely®. While the individual is consuming the bowel cleansing liquid, the patient is also consuming electrolytes included in the bowel cleansing liquid to replace in part, the electrolytes lost during the bowel cleansing procedure.

9. As stated above, in order for the gastroenterologist to be able to make an adequate examination of the colon during colonoscopy, the bowel must be relatively clean. In order to clean the bowel sufficiently for colonoscopic examination, the gastroenterologist usually asks that the patient consume a clear liquid diet for a day before the examination and take a bowel cleansing agent such as Golytely®. The purpose of the Golytely® is to induce fluid accumulation in the colon which will flush out the particulate debris from the colon leaving a clean bowel for examination. The clear liquid diet will not introduce any additional particulate matter into the bowel or add any dark colored substance to the colon which may obscure the physician's field of vision during colonoscopy.

10. As described above, an essential component of a successful bowel cleansing for colonoscopy is for the patient to consume a clear liquid diet for a period of time before the colonoscopy is performed. Chicken broth is a popular item for a clear

liquid diet in anticipation of a colonoscopy. As shown in Exhibit A attached hereto, chicken broth contains little nutritional value and no potassium, magnesium, bicarbonate, phosphate or calcium electrolytes.

11. Likewise, Jello which is a popular clear liquid diet choice is devoid of electrolytes as shown in Exhibit B attached hereto. Jello is composed of artificial sweeteners and gelatin which is a mixture of certain amino acids. No electrolytes are included in Jello.

12. Most clear liquid diet powders are simply dehydrated powders originating from substances such as chicken broth. As mentioned above chicken broth and chicken broth powder for a clear liquid diet are free of electrolytes.

13. It is important that the patient comply with the physicians orders regarding the steps necessary to obtain a clean bowel. Failure to follow the physicians orders may result in a bowel which is not clean and in which a suboptimal examination only is possible. Under that circumstance the patient is usually asked to repeat the bowel cleansing procedure and return to the clinic for the colonoscopy. One of the reasons for lack of patient compliance with the bowel cleansing procedure is the relative unpalatability of the bowel cleansing liquid such as Golytely®. Because of its salty taste some patients find Golytely® and similar preparations difficult or impossible to drink resulting in inadequate bowel preparation. To mask the salty taste of Golytely®, artificial flavors can be added to improve the palatability of the bowel cleansing preparation. The artificial flavors come in flavor packs which are provided by the manufacturer of the bowel cleansing agent. The flavor packs do not include any electrolytes which might affect the electrolyte composition of the bowel cleansing agent.

As shown in Exhibit C attached hereto and incorporated herein by reference, Nulytely®, a bowel cleansing preparation is provided with cherry, lemon-lime, or orange flavor packs to be added to the Nulytely® preparation to improve palatability of the Nulytely®. Addition of the flavoring does not change the concentration of the active ingredients of Nulytely® as shown in comparing Nulytely® without flavoring with Nulytely® with either cherry, lemon-lime or orange flavoring as shown in Exhibit C.

14. The bowel cleansing preparation Colyte may also be used with flavor packs as shown in Exhibit D which is attached hereto. Like the addition of flavor packs to Nulytely®, the addition of flavor packs to Colyte® does not affect the active ingredients of that bowel cleansing preparation (see Exhibit D). The orange flavor pack is composed of hypromellose, natural and artificial orange powder, saccharin sodium, and colloidal silicon dioxide. The other flavor packs are similarly composed with the exception that they may contain flavorings for citrus berry, lemon-lime, cherry and pineapple. The orange, citrus berry, lemon-lime and pineapple flavor packs supplied with Colyte® do not contain any electrolytes and do not change the composition of the active ingredients in the Colyte® bowel cleansing preparation. Since flavor packs and clear liquid diets are lacking electrolytes, the only electrolytes provided to a patient are those electrolytes added to the PEG preparation used for bowel cleansing.

15. I have read patent No. WO 98/43654 entitled "Non-aqueous Colonic Purgative Formulations" which is attached hereto as Exhibit E in which the inventor describes, in some detail the use of various magnesium salts, sodium sulfate, potassium tartrate, sodium tartrate, magnesium tartrate and various mixtures of the aforementioned salts for bowel cleansing preparations in anticipation of colonoscopy

and other procedures. On page 11 of the patent the invention suggests the use of various compounds either alone or in conjunction with polyethylene glycol as a bowel cleansing preparation. The compounds listed therein include sodium phosphate, sodium sulfate, sodium bicarbonate, sodium chloride, potassium chloride, magnesium hydroxide, magnesium citrate, magnesium lactate, sorbitol, magnesium carbonate hydroxide, phenolphthalein, bisacodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium, tragacanth, bran, potassium sodium tartrate, castor oil, anthraquinone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate, mineral oil and other compounds described as useful in bowel cleansing preparations. However, the inventor provides no information whatsoever regarding the concentration of the compound either alone or in combination with another compound which would comprise a safe and effective bowel cleansing preparation. Further, the inventor provides no information whatsoever as to the recommended dosage, duration of the treatment or contraindications related to use of any of these compounds. Because of the unpredictability of the effect of any of these compounds on the human body, no reasonable gastroenterologist would consider using any of these compounds either alone or in combination with another compound as a bowel cleansing preparation without information regarding the appropriate concentration of the compounds, dosage and duration of treatment. There simply is insufficient information for a reasonable gastroenterologist to attempt to use this part of the invention without extensive testing and evaluation. Such testing would be expensive, laborious, time consuming and prone to failure because of the unpredictable effect of the aforementioned compounds on the human intestinal tract.

16. In a bowel cleansing preparation employing an isotonic solution of PEG without added electrolytes and sodium phosphate, the addition of supplemental electrolytes to the aforementioned bowel cleansing preparation would be unnecessary. In this circumstance electrolyte imbalance would be unlikely to occur because of the use of an isotonic bowel cleansing preparation. The added sodium phosphate would not be the source of potassium, magnesium, calcium, chloride, or hydrogen carbonate electrolytes. Moreover, the consumption of a clear liquid diet or the addition of flavor packs to the PEG solution would not provide any electrolytes either. Supplemental electrolytes are not required to be added to an isotonic solution of PEG and sodium phosphate.

Further affiant sayeth not.

Monroe Scheiner, M.D.

SWORN TO and SUBSCRIBED before me by Monroe Scheiner on the 19 day of December, 2007.

Notary Public in and for
The State of Florida

MARY RITA DUVALL
MY COMMISSION # DD441522
EXPIRES: August 22, 2009
Ft. Notary Discount Assoc. Co.

EXHIBIT A

NuLYTELY® With Flavor Packs

PEG-3350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution

DESCRIPTION

A white powder for reconstitution containing 420 g polyethylene glycol 3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride and one 2.0 g flavor pack (optional). When dissolved in water to a volume of 4 liters, NuLYTELY (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution) is an isosmotic solution having a pleasant mineral water taste. NuLYTELY is administered orally or via nasogastric tube as a gastrointestinal lavage. NuLYTELY Flavor Packs are available in Cherry, Lemon-Lime, Orange and Pineapple. This preparation can be used without the addition of a NuLYTELY Flavor Pack.

CLINICAL PHARMACOLOGY

NuLYTELY induces a diarrhea which rapidly cleanses the bowel, usually within four hours. The osmotic activity of polyethylene glycol 3350 and the electrolyte concentration result in virtually no net absorption or excretion of ions or water. Accordingly, large volumes may be administered without significant changes in fluid or electrolyte balance.

INDICATIONS AND USAGE

NuLYTELY is indicated for bowel cleansing prior to colonoscopy.

CONTRAINDICATIONS

NuLYTELY is contraindicated in patients known to be hypersensitive to any of the components. NuLYTELY is contraindicated in patients with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or toxic megacolon.

WARNINGS

NuLYTELY Flavor Packs are for use only in combination with the contents of the accompanying 4 liter container. No additional ingredients, e.g. flavorings, should be added to the solution. NuLYTELY should be used with caution in patients with severe ulcerative colitis. Use of NuLYTELY in children younger than 2 years of age should be carefully monitored for occurrence of possible hypoglycemia, as this solution has no caloric substrate. Dehydration has been reported in 1 child and hypokalemia has been reported in 3 children.

PRECAUTIONS

General: Patients with impaired gag reflex, unconscious, or semiconscious patients, and patients prone to regurgitation or aspiration should be observed during the administration of NuLYTELY, especially if it is administered via nasogastric tube. If a patient experiences severe bloating, distention or abdominal pain, administration should be slowed or temporarily discontinued until the symptoms abate. If gastrointestinal obstruction or perforation is suspected, appropriate studies should be performed to rule out these conditions before administration of NuLYTELY.

Information for patients: NuLYTELY produces a watery stool which cleanses the bowel before examination. Prepare the solution according to the instructions on the bottle. It is more palatable if chilled. For best results, no solid food should be consumed during the 3 to 4 hour period before drinking the solution, but in no case should solid foods be eaten within 2 hours of taking NuLYTELY.

Adults drink 240 mL (8 oz.) every 10 minutes. Continue drinking until the watery stool is clear and free of solid matter. This usually requires at least 3 liters. Any unused portion should be discarded. Pediatric patients (aged 6 months or greater) drink 25 mL/kg/hour. Continue drinking until the watery stool is clear and free of solid matter. Any unused portion should be discarded. Rapid drinking of each portion is better than drinking small amounts continuously. The first bowel movement should occur approximately one hour after the start of NuLYTELY administration. You may experience some abdominal bloating and distention before the bowels start to move. If severe discomfort or distention occur, stop drinking temporarily or drink each portion at longer intervals until these symptoms disappear.

Use of NuLYTELY in children younger than 2 years of age should be carefully monitored for occurrence of possible hypoglycemia, as this solution has no caloric substrate. Dehydration has been reported in 1 child and hypokalemia has been reported in 3 children.

Drug Interactions: Oral medication administered within one hour of the start of administration of NuLYTELY may be flushed from the gastrointestinal tract and not absorbed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic and reproductive studies with animals have not been performed.

Pregnancy: Category C. Animal reproduction studies have not been conducted with NuLYTELY. It is also not known whether NuLYTELY can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. NuLYTELY should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness of NuLYTELY in pediatric patients aged 6 months and older is supported by evidence from adequate and well-controlled clinical trials of NuLYTELY in adults with additional safety and efficacy data from published studies of similar formulations.

ADVERSE REACTIONS

Nausea, abdominal fullness and bloating are the most common adverse reactions (occurring in up to 50% of patients) to administration of NuLYTELY. Abdominal cramps, vomiting and anal irritation occur less frequently. These adverse reactions are transient and subside rapidly. Isolated cases of urticaria, rhinorrhea, dermatitis and (rarely) anaphylactic reaction have been reported which may represent allergic reactions.

Published literature contains isolated reports of serious adverse reaction following the administration of PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss Tear, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrate on chest X-ray after vomiting and aspirating PEG.

DOSAGE AND ADMINISTRATION

NuLYTELY is usually administered orally, but may be given via nasogastric tube to patients who are unwilling or unable to drink the solution. Ideally, the patient should fast for approximately three or four hours prior to NuLYTELY administration, but in no case should solid food be given for at least two hours before the solution is given.

Oral administration: Adults: At a rate of 240 mL (8 oz.) every 10 minutes, until the rectal effluent is clear or 4 liters are consumed. **Pediatric Patients (aged 6 months or greater):** At a rate of 25 mL/kg/hour, until the rectal effluent is clear. Rapid drinking of each portion is preferred to drinking small amounts continuously. **Nasogastric tube administration: Adults:** At a rate of 20-30 mL per minute (1.2-1.8 liters per hour). **Pediatric Patients (aged 6 months or greater):** At a rate of 25 mL/kg/hour, until the rectal effluent is clear.

The first bowel movement should occur approximately one hour after the start of NuLYTELY administration. Ingestion of 4 liters of NuLYTELY solution prior to gastrointestinal examination produces satisfactory preparation in over 95% of patients.

Various regimens have been used. One method is to schedule patients for examination in midmorning or later, allowing the patients three hours for drinking and an additional one hour period for complete bowel evacuation. Another method is to administer NuLYTELY on the evening before the examination.

Preparation of the solution: NuLYTELY solution is prepared by filling the container to the 4 liter mark with water and shaking vigorously several times to insure that the ingredients are dissolved. Dissolution is facilitated by using lukewarm water. The solution is more palatable if chilled before administration. However, chilled solution is not recommended for infants. The reconstituted solution should be refrigerated and used within 48 hours. Discard any unused portion.

HOW SUPPLIED

NuLYTELY, Cherry Flavor NuLYTELY, Lemon-Lime Flavor NuLYTELY, Orange Flavor NuLYTELY are available in a disposable jug, in powdered form, for oral administration as a solution following reconstitution.

NuLYTELY with Flavor Packs is supplied in a disposable jug, in powdered form, for oral administration as a solution following reconstitution. Each jug has an attached package containing 4 flavor packs; one each 2.0 g: Cherry, Lemon-Lime, Orange and Pineapple flavoring, in powdered form, for the addition of ONE pack by the pharmacist prior to dispensing.

Each jug contains:

NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

Cherry Flavor NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

Lemon-Lime Flavor NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

Orange Flavor NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

NuLYTELY with Flavor Packs: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g (optional). When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

Rx only

STORAGE

Store in sealed container at 25°C. When reconstituted, keep solution refrigerated. Use within 48 hours. Discard unused portion.

NDC 52268-400-01

Distributed by Braintree Laboratories, Inc., Braintree, MA 02185 S 12/02

NU-0635 June, 2004

LABORATORIES, INC Braintree

EXHIBIT B

NDC 0091-7036-23

Note to pharmacist: Dispense bottle and all attached flavor packs to patient. Package insert enclosed. Remove before dispensing.

colyte® with flavor packs

(peg-3350 & electrolytes for oral solution)

Rx Only PCL3827G Rev. 06/05

4 Liters

This bottle contains the following ingredients:

Polyethylene glycol 3350	240.00 grams
Sodium chloride	5.84 grams
Potassium chloride	2.98 grams
Sodium bicarbonate	6.72 grams
Sodium sulfate (anhydrous)	22.72 grams

When dissolved in sufficient water to make 4 liters, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride and 18 mEq/L polyethylene glycol 3350.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

KEEP RECONSTITUTED SOLUTION REFRIGERATED. USE WITHIN 48 HOURS. DISCARD UNUSED PORTION.

APPROXIMATE NET WEIGHT: 278 GRAMS

SCHWARZ PHARMA

4 liters

colyte® with flavor packs
(peg-3350 & electrolytes for oral solution)

4 Liters
For Gastrointestinal Lavage

DESCRIPTION: colyte® with flavor packs is a colon lavage preparation provided as water-soluble components for solution. In solution this preparation with one flavor pack added delivers the following, in grams per liter.

Polyethylene glycol 3350	60.00
Sodium chloride	1.46
Potassium chloride	0.745
Sodium bicarbonate	1.68
Sodium sulfate	5.68
Flavor ingredients	0.805

When dissolved in sufficient water to make 4 liters, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride and 18 mEq/L polyethylene glycol 3350. The reconstituted solution is isosmotic and has a mildly salty taste. This preparation can be used without the flavor packs and is administered orally or via nasogastric tube.

Each orange flavor pack (3.22 g) contains hypromellose, natural and artificial orange powder, saccharin sodium, colloidal silicon dioxide. Each citrus berry flavor pack (3.22 g) contains hypromellose, artificial citrus berry powder, saccharin sodium, colloidal silicon dioxide. Each lemon lime flavor pack (3.22 g) contains, hypromellose, natural and artificial lemon lime powder, Prosweet® Powder Natural, saccharin sodium, colloidal silicon dioxide. Each cherry flavor pack (3.22 g) contains hypromellose, artificial cherry powder, saccharin sodium, colloidal silicon dioxide. Each pineapple flavor pack (3.22 g) contains hypromellose, artificial pineapple flavor powder, Magna Sweet™, saccharin sodium, colloidal silicon dioxide.

CLINICAL PHARMACOLOGY: colyte® with flavor packs cleanses the bowel by induction of diarrhea. The osmotic activity of polyethylene glycol 3350, in combination with the electrolyte concentration, results in virtually no net absorption or excretion of ions or water. Accordingly, large volumes may be administered without significant changes in fluid and electrolyte balance.

INDICATIONS AND USAGE: colyte® with flavor packs is indicated for bowel cleansing prior to colonoscopy or barium enema X-ray examination.

CONTRAINDICATIONS: colyte® with flavor packs is contraindicated in patients known to be hypersensitive to any of the components. colyte® with flavor packs is contraindicated in patients with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or toxic megacolon.

WARNINGS: Flavor packs are for use only in combination with the contents of the accompanying 4 liter container. No other additional ingredients (e.g., flavorings) should be added to the solution. colyte® with flavor packs should be used with caution in patients with severe ulcerative colitis.

PRECAUTIONS: *General*: Patients with impaired gag reflex, unconscious or semiconscious patients and patients prone to regurgitation or aspiration should be observed during the administration of colyte® with flavor packs, especially if it is administered via nasogastric tube.

If gastrointestinal obstruction or perforation is suspected appropriate studies should be performed to rule out these conditions before administration of colyte® with flavor packs.

INFORMATION FOR PATIENTS: colyte® with flavor packs produces a watery stool which cleanses the bowel prior to examination.

For best results, no solid food should be ingested during the 3 – 4 hour period prior to the initiation of colyte® with flavor packs administration. In no case should solid foods be eaten within 2 hours of drinking colyte® with flavor packs.

The rate of administration is 240 mL (8 fl. oz.) every 10 minutes. Rapid drinking of each portion is preferred rather than drinking small amounts continuously.

The first bowel movement should occur approximately one hour after the start of colyte® with flavor packs administration.

Administration of colyte® with flavor packs should be continued until the watery stool is clear and free of solid matter. This normally requires the consumption of approximately 3 – 4 liters (3 – 4 quarts), although more or less may be required in some patients. The unused portion should be discarded.

DRUG INTERACTIONS: Oral medication administered within one hour of the start of administration of colyte® with flavor packs may be flushed from the gastrointestinal tract and not absorbed.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Studies to evaluate carcinogenic or mutagenic potential or potential to adversely affect male or female fertility have not been performed.

PREGNANCY: Category C. Animal reproduction studies have not been conducted with colyte® with flavor packs, and it is not known whether colyte® with flavor packs can affect reproductive capacity or harm the fetus when administered to a pregnant patient. colyte® with flavor packs should be given to a pregnant patient only if clearly needed.

PEDIATRIC USE: Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE: Published literature contains isolated reports of serious adverse reactions following the administration of PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss Tear, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrate on chest x-ray after vomiting and aspirating PEG.

ADVERSE REACTIONS: Nausea, abdominal fullness and bloating are the most frequent adverse reactions, occurring in up to 50% of patients. Abdominal cramps, vomiting and anal irritation occur less frequently. These adverse reactions are transient. Isolated cases of urticaria, rhinorrhea, dermatitis, and rarely anaphylaxis, angioedema, tongue edema, and face edema have been reported which may represent allergic reactions.

DOSAGE AND ADMINISTRATION: colyte® with flavor packs can be administered orally or by nasogastric tube. Patients should fast at least 3 hours prior to administration. A one hour waiting period after the appearance of clear liquid stool should be allowed prior to examination to complete bowel evacuation. No foods except clear liquids should be permitted prior to examination after colyte® with flavor packs administration.

ORAL: The recommended adult oral dose is 240 mL (8 fl. oz.) every 10 minutes (see INFORMATION FOR PATIENTS). Lavage is complete when fecal discharge is clear. Lavage is usually complete after the ingestion of 3 – 4 liters.

NASOGASTRIC TUBE: colyte® with flavor packs is administered at a rate of 20 – 30 mL per minute (1.2 – 1.8 L/hour).

PREPARATION OF colyte® with flavor packs SOLUTION:

This preparation can be used with or without the flavor packs.

1. To add flavor, tear open one flavor pack at the indicated marking and pour contents into the bottle BEFORE reconstitution. Discard unused flavor packs.
2. SHAKE WELL to incorporate flavoring into the powder.
3. Add tap water to FILL line. Replace cap tightly and mix or shake well until all ingredients have dissolved. (No other additional ingredients, e.g. flavorings, should be added to the solution.)

Note: If not using flavor packs, omit steps one and two, above.

HOW SUPPLIED: colyte® with flavor packs is supplied in 4 liter bottles with an attached package containing flavor packs. Each 4 liter bottle contains polyethylene glycol 3350 240 g, sodium chloride 5.84 g, potassium chloride 2.98 g, sodium bicarbonate 6.72 g, sodium sulfate (anhydrous) 22.72 g. This preparation is supplied in powdered form, for oral administration as a solution.

colyte® with flavor packs	4 liter	NDC 0091-7036-23

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

KEEP RECONSTITUTED SOLUTION REFRIGERATED. USE WITHIN 48 HOURS. DISCARD UNUSED PORTION.

Also available as:

colyte®	4 liter	NDC 0091-4401-23

SCHWARZ PHARMA, Inc.
Milwaukee, WI 53201, USA

NDC 0091-7036-23

colyte® with flavor packs

(peg-3350 & electrolytes for oral solution)

Rx Only PCL3827G Rev. 06/05

Instructions for Pharmacist:
Dispense bottle and all attached flavor packs to the patient.

Instructions for Patient:

1. colyte® with flavor packs can be used with or without the addition of one flavor pack.
   a. If you prefer an unflavored solution, discard the flavor packs and proceed to step 5.
   b. If you prefer a flavored solution, proceed to step 2.
2. Choose **one** of the flavor packs.
3. Tear open the selected flavor pack at the indicated marking and pour the contents into the bottle **BEFORE** adding any water. Discard the unused flavor packs.
4. SHAKE WELL to incorporate flavoring into the powder.
5. Add tap water to the top of the FILL line marked 4 liters. Recap tightly and mix or shake well until the powder has completely dissolved. **No additional ingredients should be added to the solution.**
6. Refrigerate the solution until ready to drink. Chilling improves the taste. Store no longer than 48 hours.
7. For best results, solid food should not be eaten during the 3 to 4 hour period before you start drinking the solution. Never eat solid food within 2 hours of drinking the solution.
8. Drink a glassful (8 oz.) of the solution every 10 minutes. It is best to drink the solution rapidly, rather than sipping slowly. Continue drinking a glassful every 10 minutes until your watery stool is clear and free of solid matter. This normally requires drinking 3 to 4 liters (3 to 4 quarts). The bottle should be empty (4 liters consumed) or the remaining solution should be at or below the 1 liter mark (at least 3 liters consumed).

KEEP RECONSTITUTED SOLUTION REFRIGERATED.
USE WITHIN 48 HOURS. DISCARD UNUSED PORTION.

SCHWARZ PHARMA, Inc.
Milwaukee, WI 53201, USA

4 liters

EXHIBIT C

Nutrition Facts

PRINT THIS PAGE CLOSE

Natural Goodness™ Chicken Broth

Amount Per Serving (serving size) = 1 cup
Calories 15
Total Fat 0g
Sat. Fat 0g
Cholesterol 0mg
Sodium 570mg
Total Carbs. 1g
Dietary Fiber -1g
Sugars 1g
Protein 3g

%Daily Values **
Vitamin A 0%
Vitamin C 0%
Calicum 0%
Iron 0%

* The nutrition information contained in this list of Nutrition Facts is based on our current data. However, because the data may change from time to time, this information may not always be identical to the nutritional label information of products on shelf.

** % Daily Values (DV) are based on a 2,000 calorie diet.

EXHIBIT D

Jell-O

From Wikipedia, the free encyclopedia

Jell-O is a brand name belonging to USA-based Kraft Foods for a number of gelatin desserts, including fruit gels, puddings and no-bake cream pies. The brand's popularity has led to its becoming a generic term for gelatin dessert across the US and Canada.

Contents

Description

Jell-O is sold pre-made (ready to eat) or in powder form, and it is available in many different colors and flavors. The powder contains powdered gelatin and flavorings including sugar or artificial sweeteners. It is dissolved in boiling water, then chilled and allowed to set. Sometimes fruit, vegetables, whipped cream, or other ingredients are added to make often elaborate desserts that can be molded into any number of shapes. Jell-O must be refrigerated until served, and once set properly, it is normally eaten with a spoon.

The pudding line is cooked on a stovetop in hot milk, then chilled until it sets, or in the case of the instant pudding, simply dissolved in cold milk and then chilled. The no-bake pie line is generally mixed with milk and then poured into an included crust, and allowed to set in a refrigerator.

Though the word Jell-O is a name brand, it is commonly used in America as a generic name for all products of this kind.

Many vegetarians do not eat Jell-O because it contains gelatin, which is made out of animal bone.

History

Gelatin has been well known and used for many years. It was popularized in the Victorian era with spectacular and complex "jelly moulds". Previously, gelatin was sold in sheets and had to be purified,

which was very time-consuming. In 1845, industrialist Peter Cooper (who built the first American steam-powered locomotive, the *Tom Thumb*), obtained a patent (US Patent 4084) for powdered gelatin derived from the bones of geese.[1]

Forty years later the patent was sold to a LeRoy, New York-based carpenter and cough syrup manufacturer, Pearle B. Wait. He and his wife May added strawberry, raspberry, orange and lemon flavoring to the powder and gave the product its present name in 1897. Unable to successfully market their concoction, in 1899 the Waits sold the business to a neighbor, Orator Francis Woodward, for $450.

Beginning in 1902, Woodward's Genesee Pure Food Company placed advertisements in the *Ladies' Home Journal* proclaiming Jell-O to be "America's Most Famous Dessert." Within a decade, three new flavors, chocolate (discontinued in 1927), cherry and peach, were added, and the brand was launched in Canada. Celebrity testimonials and recipes appeared in advertisements featuring actress Ethel Barrymore and opera singer Ernestine Schumann-Heink.

In 1923, the newly rechristened Jell-O Company launched D-Zerta, an artificially sweetened version of Jell-O. Two years later, Postum and Genesee merged, and in 1927 Postum acquired Clarence Birdseye's frozen foods company to form the General Foods Corporation. By 1930, there appeared a vogue in American cuisine for congealed salads, and the company introduced lime-flavored Jell-O to complement the various add-ins that cooks across the USA were combining in these aspics and salads. By the 1950s, these salads would become so popular that Jell-O responded with savory and vegetable flavors such as celery, Italian, mixed vegetable and seasoned tomato. These savory flavors have since been discontinued.

In 1934, sponsorship from Jell-O made comedian Jack Benny the dessert's spokesperson.[2] At this time also was introduced a jingle (created by the agency Young & Rubicam[3]) that would be familiar over the next several decades, in which the spelling "J-E-L-L-O" was (or could be) sung over a rising five-note musical theme.

In 1936, chocolate returned to the Jell-O lineup, this time as an instant pudding made with milk. It proved enormously popular and over time other pudding flavors were added such as vanilla, tapioca, coconut, pistachio, butterscotch, egg custard, flan and rice pudding.

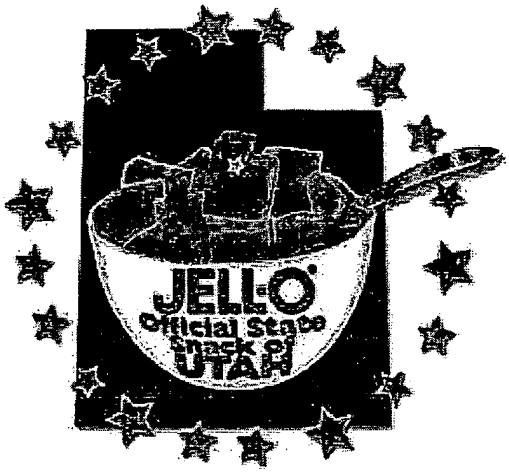
New flavors continued to be added and unsuccessful ones were removed: in the 1950s and 1960s, apple, black cherry, black raspberry, grape, lemon-lime, mixed fruit, orange-banana, pineapple-grapefruit, blackberry, strawberry-banana, tropical fruit and more intense "wild" versions of the venerable strawberry, raspberry and cherry. In 1966, the Jell-O "No-Bake" dessert line was launched, which allowed a cheesecake to be made in 15 minutes. In 1971 pre-packaged prepared pudding called Jell-O Pudding Treats were introduced. During this same period, Jell-O 1-2-3, a gelatin dessert that separated into three layers as it cooled, and Jell-O Whip 'n Chill, a mousse-style dessert, were also introduced and widely promoted; they remain available only in limited areas today.

In 1964, the slogan "There's always room for Jell-O" was introduced, promoting the product as a "light dessert" that could easily be consumed even after a heavy meal.

In 1974, comedian Bill Cosby became the company's pudding spokesperson, and continued to serve as the voice of Jell-O for almost thirty years. Over the course of his tenure as the mouthpiece for the company, he would hawk new products such as frozen Jell-O Pops (in both gelatin and pudding varieties); the new Sugar-Free Jell-O, which replaced D-Zerta and was sweetened with NutraSweet; Jell-

O Jigglers concentrated gummi snacks; and Sparkling Jell-O, a carbonated version of the dessert touted as the "Champagne of Jell-O."

In 1989, General Foods was merged into Kraft Foods by parent company Phillip Morris (now the Altria Group). New flavors were continually introduced: watermelon, blueberry, cranberry, margarita and piña colada among others. In 2001 Jell-O was declared the "Official State Snack" of Utah, with Governor Michael O. Leavitt declaring an annual "Jell-O Week."



Today, there are more than 158 products sold under the Jell-O brand name and about 300 million boxes of Jell-O gelatin sold in the United States each year,

Jell-O is also used as a substantial ingredient in a well-known dessert, the preparation of which requires a mold designed to hold Jell-O, and the depositing of small quantities of chopped fruit into the Jell-O before it hardens and takes on its typical form.

Today, LeRoy, New York, is still known as the home of Jell-O and has the only Jell-O Museum in the world located on the main road through the small town. Visitors can learn about the history of the dessert from its inception and see how it became one of the world's most recognized sweets.

Current flavors of Jell-O desserts

Gelatin

- Lemon
- Lime
- Berry Blue
- Grape
- Raspberry
- Strawberry-Banana
- Wild Strawberry
- Black Cherry
- Cranberry
- Cherry
- Mixed Fruit
- Strawberry
- Strawberry-Kiwi
- Watermelon
- Peach
- Orange
- Apricot
- Cranberry-Raspberry
- Pineapple
- Tropical Berry(prepared only)
- Green Apple
- Margarita (seasonal)
- Piña Colada (seasonal)
- Strawberry Daiquiri (seasonal)
- Fruit Fiesta
- Melon Fusion
- Tropical Fusion

Pudding

- Pistachio
- Chocolate
- Vanilla
- Cookies 'n Creme (Oreo)
- Lemon
- Cheesecake
- Egg Custard
- Coconut Cream
- White Chocolate
- Rice
- French Vanilla
- Banana Cream
- Smore
- Lemon
- Pumpkin Spice (seasonal)
- Chocolate-Vanilla Swirl (prepared only)
- Vanilla-Caramel (prepared only)
- Tapioca (prepared only)
- Dulce De Leche
- Double Chocolate (prepared only)
- Creamy Caramel (prepared only)

- Butterscotch
- Devil's Food
- Chocolate Fudge
- Chips Ahoy!

Discontinued flavors of Jell-O brand desserts

- Mango
- Cola
- Chocolate
- Apple
- Strawberry-Kiwi
- Concord Grape
- Wild Cherry
- Wild Raspberry
- Tropical Fruit
- Orange-Banana
- Orange-Pineapple
- Black Raspberry
- Blackberry
- Fruit Mold Supreme
- Pineapple-Grapefruit
- Lemon-Lime
- Strawberry Punch
- Cranberry-Strawberry
- Celery
- Mixed Vegetable
- Italian Salad
- Coffee
- Seasoned Tomato
- Sparkling White Grape
- Sparkling Berry
- Sparkling Mandarin Orange
- Orange-Coconut (pudding)
- Plain

Cultural references

Stage and Screen

Perhaps the earliest cultural reference to Jell-O was in the lyrics of "Cockeyed Optimist" from the musical *South Pacific* (Rodgers and Hammerstein, 1949) when Nellie sings "I could say life is just a bowl of Jell-O". Forty years later, it was mentioned in the film *Ghostbusters 2*. When Winston is reminded that a supernatural 'goo' resembles Jell-O, he remarks that he hates Jell-O. Peter Venkman responds, "There's always room for Jell-O". In the popular American TV series *The Office* (2005) Jim Halpert has encased Dwight Schrute's and Andy Bernard's office supplies in Jell-O. In the original UK-based show (2001) Tim Canterbury did the same to Gareth Keenan, though they referred to the dessert by the common UK term "jelly".

Commercials

Comedian Bill Cosby is usually associated with Jell-O and, more famously, Jell-O pudding as he has appeared in many commercials promoting both. Shows like *MAD TV* and *SNL* parody Cosby, using Jello references like "pudding pop". In the 1960s, the cast of the popular sitcom *Hogan's Heroes* did a commercial with Carol Channing featuring the gang having Jell-O for dessert.

Other TV appearances

Samantha Carter of *Stargate SG-1* has been seen to enjoy blue Jell-O on numerous occasions. Jell-O powder was a primary ingredient in the green slime for the 1980s cult TV hit, *You Can't Do That on Television.*

Jello Biafra

Eric Reed Boucher (born June 17, 1958) originally the lead singer and songwriter for San Francisco punk rock band Dead Kennedys and now a political activist, combined the brand name Jell-O with the name of the short lived country of Biafra (which attempted to secede from Nigeria in 1966) to create his

stage name, Jello Biafra. After four years of fighting and horrific starvation in Biafra, Nigeria regained control of the nascent Biafran state. Jello Biafra created his name as an ironic combination of a nutritionally poor mass-produced food product and mass starvation. He says he likes how two ideas clash in people's minds.

See also

- Jell-O Belt

References

1. ^ http://www.google.com/patents?vid=USPAT4084
2. ^ http://findarticles.com/p/articles/mi_qn4188/is_20060628/ai_n16505923
3. ^ http://www.lubbockonline.com/stories/091000/bus_091000020.shtml

Further reading

- Kraft Foods: History of Jell-O (http://www.kraftfoods.com/jello/explore/history/)
- Gelatin Manufacturers Institute of America (http://www.gelatin-gmia.com/)
- Watch a Jell-O commercial by the Fifth Dimension (http://www.youtube.com/watch?v=53hQAPBuW5o), circa 1969 on Youtube
- The World's Only JELL-O Museum (http://www.jellomuseum.com/)

Kraft brands

Capri Sun | Crystal Light | Dairylea | General Foods | **Jell-O** | Kool-Aid | Kraft Dinner | Maxwell House | Oscar Mayer | Post Cereals | Tang | Toblerone | Vegemite

Categories: American cuisine | Canadian cuisine | Desserts | Genericized trademark | Kraft brands | Animal products

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(54) Title: NON-AQUEOUS COLONIC PURGATIVE FORMULATIONS

(57) Abstract

Orally administered colonic purgative formulations and methods of their use for effecting partial or complete purgation of the colon in mammals, the formulations consisting of non-aqueous admixtures of a purgative salt selected from the group consisting of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate and mixtures thereof, administered in tablet or capsule form in purgative effective concentrations. Preferred embodiments make use of at least one or more magnesium phosphate salts, more preferably dibasic magnesium phosphate; other preferred embodiments include the addition of binders, dispersants and buffers which do not adversely affect osmolality or effectiveness of the purgative formulations.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 33/42, 33/14, 33/08, 33/06, 33/04
US CL :424/601, 681, 689, 692, 697, 709
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, BIOSIS, MEDLINE, EMBASE, WPIDS, USPATFULL- salts and additional ingredients claimed for treatment of the bowel or colon as a purgative or laxative.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,232,698 A (HORD) 03 August 1993, the abstract and columns 3 and 5-6.	1-25
Y	FINGL, E. Laxatives and Cathartics. In: GOODMAN GILMAN'S: The Pharmacological Basis of Therapeutics (6th Ed.). New York: published by Macmillan. 1980, pages 1002-1005, see entire document.	1-25
Y	Pharmacotherapy: A Pathophysiologic Approach. edited by DIPIRO, J.T. et al. New York: Elsevier. 1989, pages 476-478.	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"P"	document published prior to the international filing date but later than the priority date claimed		

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NON-AQUEOUS COLONIC PURGATIVE FORMULATIONS

This invention relates to colonic purgative formulations based upon inorganic salts and, more particularly, to nonaqueous purgative formulation compositions which may be administered in capsule or tablet form for preparing the colon for surgical or diagnostic procedures.

BACKGROUND OF THE INVENTION

In certain medical procedures, for example, colonoscopy, radiographic examination and in preparation for patients undergoing bowel surgery, it is often critical that the colon be emptied as completely as possible. For example, in order to obtain satisfactory radiographs it is often essential that the intestines be cleansed sufficiently, particularly with regard to the elimination of gas from the colon. The same condition also applies when the colon is preoperatively prepared for surgery, or for diagnostic procedures such as colonoscopies, in which case it is also necessary to remove fecal waste materials.

Typical prior art colonic purgative procedures involved the emptying of the colon using water enemas wherein large quantities of water are introduced into the colon to induce emptying-the contents of the colon being expelled in the form of a suspension. It has, however, been recognized that the use of enemas may be injurious to the patient. In view of the hazard and disadvantages associated with large volume water enemas, an alternative has been to introduce enemas of a hypertonic aqueous solution typically, of various salts to substitute for the large water enema. The advantage of these salt formulations is that they require significantly less water volume in their administration. The effect of these hypertonic enemas is based on the increase of the osmotic pressure in the colon which, in turn, may have undesirable side effects, particularly, if the hypertonic solution diffuses through the wall of the colon and disturbs the fluid balance of the body. Although this is an improvement over simple water enemas, this potential side effect limits the utility of these compositions.

Additionally, many enema compositions in aqueous solutions include a contact laxative agent causing peristalsis in the colon with sufficient concentration of laxation without the need for excessive amounts of water. Such compositions often include salt

mixtures and may also contain chemical agents such as propylene glycol and non-ionic wetting agents such as polyether alcohols. The problems with these formulations, aside from the often problematic methods of enema administration, are incomplete evacuation of the bowels, repeat administrations and the inclusion of certain chemicals which may have an irritating effect on the colonic walls. Furthermore, because it is often necessary to employ repeated washout enemas to clear the colon effectively, the potential for such chemical irritation is greatly increased.

More recently, a number of orally administered liquid pharmaceutical compositions have been developed for use as gastrointestinal washes for diagnostic purposes or for use as cathartic laxatives. Such preparations consist of aqueous solutions of polyethylene glycol and electrolytes suchs as sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride. These orally administered compositions are particularly useful in the rapid washing of the colon for diagnostic purposes. For example, when a powerful gastrointestinal wash is required, such preparations are generally administered in a quantity of about four liters, the composition being typically formulated according to the following: polyethylene glycol 59 g., sodium sulphate 5.68 g., sodium bicarbonate 1.69 g., sodium chloride 1.46 g., potassium chloride 0.745 g. and water to make up one liter.
Laxation and relatively thorough evacuation is often significantly improved over enema formulations, and generally without the problems often encountered with enema administrations.

The advantages of using these preparations over other orally administered preparations are a drastic reduction in wash time (from 3-2 days to 4-5 hours) and the minimization of water and electrolyte losses. The advantages which these types of solutions provide are derived from two essential characteristics of the preparation, namely, its isoosmoticity with the physiological liquids, and the balance of the ion species in solution, so as to compensate the transport mechanisms which regulate gastrointestinal absorption. These characteristics result in substantial isotonicity between the preparation and the intracellular and extracellular fluids at the tissues of the digestive

tubes walls.

Commercially available products embodying these formulations typically utilize a polyethylene glycol formula serving as a non-absorbable osmotic agent with a mixture of electrolytes for replenishment, so that patients do not become dehydrated. Patients are required to ingest a significant amount of volume for purgation which may include a one eight ounce glass every ten minutes for a total of one gallon of fluid. Due to the fact that the volume is so high, use of this type of formulation is frequently associated with distention and nausea on a significant scale.

Another serious drawback of these known preparations is their unpleasant, bitter, saline taste which in the more sensitive patients can lead to vomiting- thereby preventing ingestion. However, as the requirement of solution isotonicity is necessary to obtain the aforesaid advantages, the introduction of water soluble adjuvants, for example, to alter taste, must be avoided. Even the most common natural sweeteners such as glucose, fructose, saccharose, and sorbitol could change the osmolarity of these solutions and the inclusion of such adjuvants are generally expressly prohibited. Moreover, even altering the unpleasant taste of these preparations with artificial sweeteners or flavorants in these commercial preparations must be avoided as they could also alter the critical isotonicity.

Furthermore, in the aforesaid preparations of the known art, it is also well recognized that the addition of appreciable quantities of substances which can be fermented by the intestinal flora should be avoided. This is because gas could form which could be extremely dangerous in the case of colonoscopy with electrocautery.

In an attempt to avoid the problems associated with the high volume types of preparations, other investigators have utilized ingestible preparations which consist of aqueous solutions of phosphate salts. The aqueous phosphate salt solution produces a tremendous osmotic effect on the intra-luminal contents of the bowel and therefore, evacuation of the bowel occurs with a tremendous increase in the influx of water and electrolytes into the colon. This has been developed for the express purpose of

decreasing the volume required in colonic purgations. One such preparation basically is comprised of 480 grams per liter monobasic sodium phosphate and 180 grams per liter dibasic sodium phosphate in stabilized buffered aqueous solution and is sold under the brand name Fleets Phospho-Soda™. Patients are typically required to take two three ounce dosages of this preparation, separated by a three hour interval for a total of six ounces, which is a significant reduction compared to large volumes required by other high volume preparations.

The major short-coming of such concentrated aqueous phosphate solution administration is that the aqueous solution is extremely unpalatable, so much so that the recommended dosage form is administered ice cold so as to minimize the objectionable saline taste. Often, patients complain of severe nausea and vomiting, secondary to the extremely salty taste of the preparation. Frequently, patients cannot even tolerate the ingestion of this preparation at the initial dose and often the second dose becomes even more problematic due to the unpalatable extremely salty taste, even when the taste is partially masked by the use of flavoring agents. Thus, while concentrated purgation solutions represent a slight improvement over other methods of inducing purgation, the short comings of these solutions are readily apparent.

From the foregoing, it can be seen that it is desirable to have an orally administered colonic purgative formulation which may be easily and conveniently administered and which avoids the problems and objectionable tastes of known formulations. It can also be seen that it is desirable to have such a purgative formulation which may be administered without large volumes of water necessary in conventional formulations and which avoids other potentially irritant chemicals or chemicals which could effect osmolality.

It is an object of the present invention to provide easily and conveniently administered dosage formulations of effective colonic purgatives.

It is yet another object of the present invention to provide a colonic purgative

formulation which provide purgative activity at lower dosages of salt than prior art sodium phosphate tablets.

It is still another object of the present invention to provide a method of administering a colonic purgative with a minimum amount of patient discomfort.

Yet another object of theinstant invention is to provide a formulation for colonic purgatives which avoids the addition of other components which may be broken down by intestinal flora.

These and other objects and advantages of the invention will be evident after reading the following description.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to colonic purgative formulations in which are contained purgative active amounts of a salt selected from the group consisting of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, potassium tartrate, sodium tatrate and magnesium tartrate and mixtures, thereof, in a stable, nonaqueous tablet dosage form. In one preferred embodiment, the dosage formulation comprises dibasic magnesium phosphate ($MgHPO_4$). In preferred embodiments, the formulation comprises an effective amount of a purgative salt, preferably, dibasic magnesium phosphate, comprising approximately 0.05 to about 2.0 grams per kilogram body weight which may be conveniently administered to the patient in a tablet or capsule form. Preferably, the patient dosage of the purgative salt falls within the range of about 0.1 to about 1.2 grams per kilogram body weight, magnesium phosphate salts, more preferably about 0.2 to 0.7 grams per kilogram bodyweight. In preferred embodiments according to the present invention, the salt is magnesium hydrogen phosphate (dibasic magnesium phosphate) or a mixture of magnesium hydrogen phosphate and magnesium dihydrogen phosphate (monobasic magnesium phosphate).

In other preferred embodiments, the formulation may be a mixture of dibasic magnesium phosphate and monobasic magnesium phosphate wherein the total amount of the two salts falls within the above ranges. The formulations according to the present invention may further include tablet binders, dispersants and/or buffering agents. Further, in other embodiments, the formulation may include tribasic magnesiium phosphate in addition to either monobasic or dibasic magnesium phosphate, or both, within the above ranges.

DETAILED DESCRIPTION OF THE INVENTION

The term "patient" is used throughout the specification to describe an animal, preferably a human, to whom treatment with the compositions according to the present invention is provided. For treatment of those conditions which are specific for a specific animal such as a human patient, the term patient refers to that specific animal. In most instances in the description of the present invention, the term "patient" will refer to human patients.

The term "salt" or "purgative salt" is used throughout the present application to describe one or more of the anhydrous compounds which find use in purgative products according to the present invention. Salts according to the present invention may be found in their anhydrous form or as in hydrated crystalline form (i.e., complexed or crystallized with one or more molecules of water). Purgative salts for use in the present invention include, for example, $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate, or mixtures, thereof. Preferred salts include the magnesium phosphate salts, with a particularly preferred salt being magnesium monohydrogen phosphate (dibasic magnesium phosphate) or a mixture of magnesium monohydrogen phosphate and magnesium dihydrogen phosphate salts. The magnesium phosphate salts are preferred for use in the present invention because of the dual effect which is produced by both the phosphate anion and the magnesium cation. As a result of this dual action, the magnesium phosphate salts may be utilized in the present invention in amounts which are considered "low dose", i.e. in an amount

which is unexpectedly low based upon or compared to other salts, such as sodium phosphate salts which find use in anhydrous purgative formulations.

The term "purgative effective amount" or "purgative effective dosage" is used throughout the specification to describe the amount or concentration of purgative salts used in the present invention which is effective for producing a purgative effect, i.e., the elimination or evacuation from the intestines of its contents. In the case of the magnesium phosphate salts, these salts have unexpectedly been found to be advantageously employed in amounts which are significantly lower than for the sodium phosphate salts. The term "purgative active" is used to describe salts according to the present invention which exhibit biological or pharmacological activity in the form of purgative activity. In the case of cathartic compounds/compositions which may be used in combination with the present compounds or related prior art compounds such as mono-, di- and tribasic salts of sodium phospate, the term "effective amount" is that amount which is deemed effective for producing an intended result, whether the intended result or effect is a cathartic or a purgative effect.

The term "anhydrous" is used throughout the specification describe the form in which the purgative salts according to the present invention are administered. Anhydrous formulations are those which essentially have excluded water from the formulations, except, in such instances where the salt is hydrated or otherwise complexed with small amounts of water.

The physiology of intestinal secretion and absorption is generally well known as reflected in the reported literature. While not being limited by way of theory, Applicant's invention is believed to function by creating an increase in intra-luminal fluid of the small bowel to a significant degree and/or creating favorable osmotic conditions in the intestine which allows for a net secretion of sodium and water into the lumen. In addition, in certain embodiments which utilize magnesium phosphate anions, the osmotic effect of the phosphate anions in combination with the motility enhancing effect of the magnesium cations create a synergistic purgative effect which makes the

magnesium phosphate salts particularly preferred for use in the present invention. This allows for tremendous fluxes of water to be present within the gastrointestinal lumen which exhibits increased motility, thus producing an unexpectedly effective purgative effect.

In producing formulations according to the present invention, in a preferred embodiment, the present invention consists of a dry admixture of dibasic magesium phosphate or a mixture of monobasic and dibasis magnesium phosphate in an anhydrous state. Formulations according to the present invention may be prepared by placing one or more of the purgative salts according to the present invention, in pharmaceutical form, in a ribbon blender or other similar mung apparatus to effect complete mixing of the components. Additional constituents such as tablet binders, dispersants and/or buffering agents in the range of approximately 0.025% to 25% by weight, more preferably about 1% to 5% by weight, may also be included in the admixture. The formulations may be formulated in tablet or capsule form for oral delivery to a patient.

In preferred embodiments according to the present invention, phosphate salts are used, preferably magnesium phosphate salts and more preferably magnesium monohydrogen phosphate or mixtures of magnesium monohydrogen phosphate and magnesium dihydrogen phosphate. In other preferred embodiments, the amount of magnesium dihydrogen phosphate may be substantially reduced or eliminated in its entirety. In these formulations, dibasic phosphate or tribasic phosphate salts such as magnesium dibasic phosphate and magnesium tribasic phosphate may be used alone or in combination as the principal or exclusive form of phosphate in the formulation, while maintaining a complete purgative effect. Other phosphate salts according to the present invention may also be used, but these salts are less preferred. Upon ingestion, phosphate salts cause a tremendous amount of water to be drawn into the gut. This influx of water causes an increase in intraluminal pressure, which in turn exerts a mechanical stimulus causing an increase in intestinal motility. The purgative effect of the phosphate salts appears to be proportionately related to the increase in the anionic state of the phosphate salt and may be differentiated in their mode of action from other salt formulations which

are capable of producing a limited cathartic effect. One such salt, magnesium sulfate, for example, exerts its effect via the magnesium cation which causes hypermotility of the gut. Although not being limited by way of theory, it is believed that the magnesium phosphate salts according to the present invention exert their unexpected enhanced activity by virtue of the combined activity of the phosphate anion and magnesium cation, creating a dual effect.

The admixture of the present invention is formed into an easily administered dosage form, such as tablets or into capsules by methods well known in the art. As used herein, the term admixture refers to a formulation which includes at least one purgative salt, preferably a phosphate or magnesium salt, more preferably at least one magnesium phosphate salt and even more preferably magnesium hydrogen phosphate (alone or in combination with another purgative salt, preferably a magnesium phosphate salt) and at least one other component including other phosphate salts or other additives as disclosed herein. When forming tablets containing the purgative formulation, it will be appreciated that the salts can be compressed into a uniform mixture and can optionally include inert diluents such as a tablet binder. Preferably, the tablet binder is a pharmaceutically acceptable binder and is one which produces no appreciable osmotic effects. Examples of useful binders include non-ionic detergents from the Pluronic™ series, such as Pluronic F-68 (a trademark of BASF-Wyandotte Chemicals, defined as a condensate of ethylene oxide with a condensate of propylene oxide and propylene glycol), related non-ionic surfactants, and mechanical adhesives such as polyvinyl alcohol and sodium carboxymethylcellulose, among numerous others. Microcrystalline cellulose (MCC) may also be used to enhance the compactability of the purgative salts into the tablet or capsule form. One of ordinary skill may readily modify the additives combined with the purgative salts according to the present invention in order to optimize the formulations for oral delivery.

In another preferred embodiment of the instant invention, the tablet or capsules may also include inert dispersal agents which will facilitate dissolution of the tablet or capsule contents in the stomach of the patient. Preferably, the dispersal agent is a

pharmaceutically acceptable dispersant and is one which also produces no appreciable osmotic effects. Examples of acceptable dispersants include microcrystalline cellulose (which is also useful as a compacting agent) and anhydrous lactose. A preferred dispersal agent is AC-DI-SOL, a cross-linked starch.

In another preferred embodiment of the present invention, the preferred composition may also include a buffering agent to minimize any acid imbalance which may accompany ingestion of the purgative formulation of Applicants' invention. Suitable buffering agents include magnesium hydroxide, aluminum hydroxide, calcium carbonate and magnesium carbonate.

An important characteristic of the colonic purgative formulations of the instant invention is that they function effectively as purgatives when administered in low volume dosages, as compared to known formulations. In this manner, 2 to 12 tablets, and preferably 4 to 10 tablets per dose, depending on tablet size and weight, with only fluids necessary to assist in swallowing the tablets, will provide complete purgation. The dosage may be administered in a single application but may be preferably administered in two applications separated by approximately 2 to 4 hours. Use of the formulations of this invention in tablet form effectively removes the colonic contents without requiring injection of large quantities of water. Conventional purgative products historically and currently available on the market have had to employ much greater liquid volumes in order to obtain the desired result.

A further aspect of the present invention relates to the inclusion of purgative salts disclosed herein in combination with other prior art purgatives and/or laxative compounds and/or compositions. Thus, any one or more of the purgative salts according to the present invention in an effective amount may be combined with and/or co-administered with an effective amount of any one or more of numerous other purgative salts and/or laxative compounds including, for example, sodium phosphate salts (mono-, di- and tribasic salts) of U.S. patent no. 5,616,346 to Craig Aronchick, related preparations of aqueous sodium phosphate salts, e.g. polyethylene glycol, electrolytes

such as sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride, among others, including $Mg(OH)_2$, citrate salts such as magnesium citrate, sorbitol, and magnesium carbonate hydroxide, among numerous others.

In still another aspect of the present invention, sodium phosphate salts (mono-, di- and tribasic) may be combined with any one or more of the compounds of the present invention or of the prior art may be combined in effective amounts to produce potentially synergistic purgative activity. Thus, in this aspect of the present invention, the sodium phosphate salts (mono-, di- and tribasic salts) as disclosed by Aronchick, U.S. patent no. 5,616,346, are combined with any one or more of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate, or mixtures, thereof of the present invention or alternatively, the prior art phosphate salts of Aronchick may be combined with any one or more of prior art purgative or laxative compounds or compositions including, for example, aqueous sodium phosphate salts, polyethylene glycol or aqueous polyethylene glycol, electrolyte solutions such as sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride, among others, including $Mg(OH)_2$, citrate salts such as magnesium citrate, lactate salts such as magnesium lactate, sorbitol, magnesium carbonate hydroxide, diphenylmethanes such as phenolpththalein and bisacodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium (plantago) preparations, tragacanth and related natural gums, bran and other fibers, potassium sodium tartrate, castor oil, anthraquinones such as senna, cascara sagrada, aloe and danthrone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate and minerol oil, among others, in effective amounts, in order to produce a purgative and/or laxative composition which evidences synergistic activity in comparison to the prior art compositions and/or compounds which are used alone. In this aspect of the present invention, a combination of the above-described compounds is administered to a patient in an amount effective to produce a purgative or cathartic/laxative effect. These compounds/compositions may be administered in solid or liquid (aqueous) form and are taken orally to produce the intended effect. One of ordinary skill may readily determine the amount and types of compounds/compositions to be used in treating a particular patient. The combinations of compounds/compositions

as described above may be administered at the same time, or within the period of activity of a first compound/composition in order to enhance the effect of the first compound(s) or composition(s) used. In this sense combinations of compounds or compositions as described herein may be co-administered to produce an enhanced purgative effect.

The foregoing description is illustrative of the preferred embodiments shown. It is not intended to limit the present invention to the specific formulations shown and described, but instead it will be appreciated that adaptations and modifications will become apparent from the present disclosure and are intended to be within the scope of the claims.

What I claim is:

1. An orally administerable non-aqueous composition capable of inducing purgation of the colon of a patient comprising a purgative effective amount of a nonaqueous admixture of a salt selected from the group consisting of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate and mixtures, thereof.

2. The composition according to claim 1 wherein said salt is a phosphate salt.

3. The composition according to claim 1 wherein said phosphate salt is selected from the group consisting of monobasic magnesium phosphate, dibasic magnesium phosphate and tribasic magnesium phosphate.

4. The composition of Claim 2 wherein said phosphate salt is dibasic magesium phosphate or a mixture of dibasic magenesium phosphate and monobasic magnesium phosphate.

5. The composition of Claim 1 wherein said salt is included in an amount ranging from about 0.05 grams per kilogram body weight to about 2.0 grams per kilogram body weight of said patient.

6. The composition of Claim 3 wherein said magnesium phosphate salt is included in an amount ranging from about 0.1 to about 1.2 grams per kilogram body weight of said patient.

7. The composition of Claim 3 wherein said magnesium phosphate salt is dibasic magnesium phosphate included in an amount ranging from about 0.2 to about 0.7 grams per kilogram body weight of said patient.

8. The composition of Claim 1 further comprising a buffering agent selected

from the group consisting of magnesium hydroxide, aluminum hydroxide, calcium carbonate and magnesium carbonate.

9. The composition of Claim 3 further comprising a buffering agent selected from the group consisting of magnesium hydroxide, aluminum hydroxide, calcium carbonate and magnesium carbonate.

10. The composition of Claim 1 further comprising a dispersal agent selected from the group consisting of anhydrous lactose, microcrystalline cellulose and ACDI-SOL.

11. The composition of Claim 9 further comprising a dispersal agent selected from the group consisting of anhydrous lactose, microcrystalline cellulose and ACDI-SOL.

12. The composition of claim 1 further comprising a binding agent selected from the group consisting of non-ionic detergents, mechanical adhesives and microcrystalline cellulose.

13. The composition of claim 9 further comprising a binding agent selected from the group consisting of non-ionic detergents, mechanical adhesives and microcrystalline cellulose.

14. A method of inducing purgation of the colon in a patient comprising the steps of:

(a) preparing a non-aqueous admixture of a purgative salt selected from the group consisting of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate and mixtures, thereof to form a purgative formulation;

(b) forming an orally administrable dosage form of said purgative formulation;

(c) orally administering a purgative effective dosage of said formulation to a patient; and

(d) allowing said administered dosage to induce purgation.

15. The method of Claim 10 wherein step (a) further includes the step of adding to said purgative formulation at least one member selected from the group consisting of buffering agents, dispersal agents and binders .

16. The method of Claim 14 wherein said orally administrable dosage form is selected from the group consisting of gelatin capsules and tablets.

17. The method of Claim 14 wherein the admixture formed in step (a) includes a purgative salt selected from the group consisting of dibasic magnesium phosphate, monobasic magnesium phosphate and mixtures, thereof.

18. The method of Claim 17 wherein said purgative salt is dibasic magnesium phosphate included in an amount ranging from about 0.2 grams per kilogram body weight to 12.0 grams per kilogram body weight.

19. The method of Claim 17 wherein said purgative salt is a mixture of dibasic magnesium phosphate and monobasic magnesium phosphate included in an amount ranging from about 0.2 grams per kilogram body weight to 12.0 grams per kilogram body weight.

20. The method of Claim 18 wherein said dibasic magnesium phosphate is administered at a rate of from about 0.2 grams per 1dlogram body weight to 0.7 grams per kilogram body weight.

21. The method of Claim 14 wherein step c) is repeated at least once.

22. The method of Claim 17 wherein step c) is repeated at least once.

23. An orally administerable non-aqueous composition capable of inducing

purgation of the colon of a patient comprising a purgative effective amount of a nonaqueous admixture of a salt selected from the group consisting of $Mg_3(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, Na_2SO_4, sodium tartrate, potassium tartrate, magnesium tartrate and mixtures, thereof in combination with a purgative effective amount of at least one sodium phosphate salt selected from the group consisting of monobasic sodium phosphate, dibasic sodium phosphate and tribasic sodium phosphate.

24. The composition according to claim 23 wherein said composition further includes an effective amount of at least one composition selected from the group consisting of aqueous sodium phosphate salts, polyethylene glycol, aqueous polyethylene glycol, aqueous solutions of sodium sulfate, sodium bicarbonate, sodium chloride or potassium chloride, $Mg(OH)_2$, citrate salts such as magnesium citrate, lactate salts such as magnesium lactate, sorbitol, magnesium carbonate hydroxide, phenolpththalein, bisacodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium, tragacanth, bran, potassium sodium tartrate, castor oil, senna, cascara sagrada, aloe, danthrone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate, minerol oil, and mixtures, thereof.

25. An orally administerable non-aqueous composition capable of inducing purgation of the colon of a patient comprising a purgative effective amount of a nonaqueous admixture of a sodium phosphate salt selected from the group consisting of monobasic sodium phosphate, dibasic sodium phosphate and tribasic sodium phosphate in combination with an effective amount of at least one composition selected from the group consisting of aqueous sodium phosphate salts, polyethylene glycol, aqueous polyethylene glycol, aqueous solutions of sodium sulfate, sodium bicarbonate, sodium chloride or potassium chloride, $Mg(OH)_2$, citrate salts such as magnesium citrate, lactate salts such as magnesium lactate, sorbitol, magnesium carbonate hydroxide, phenolpththalein, bisacodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium, tragacanth, bran, potassium sodium tartrate, castor oil, senna, cascara sagrada, aloe, danthrone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate, minerol oil, and mixtures, thereof.